REMARKS

Status of the Application

At the time the Office Action was mailed, claims 1-24 were pending in the application. Claim 18 was rejected under 35 U.S.C. § 102(b). Claims 1-17 and 19-24 were rejected under 35 U.S.C. § 103.

In this amendment, claims 1, 5, and 13 have been amended, claims 18-24 have been canceled, and no claims have been added. Therefore claims 1-17 remain before the examiner for consideration.

Rejection Under 35 U.S.C. § 102(b)

Claim 18 was rejected as being anticipated by Wheeler et al., for reasons set forth in the Office Action of February 27, 2002. Claim 18 having been canceled by this amendment, this rejection is rendered moot. Therefore withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 1-17 and 19-24 were rejected under 35 U.S.C. 103 as being unpatentable over Wen et al. (U.S. Patent 6,066,675) ("Wen") and Sallman et al. (U.S. Patent No. 5,891,913) ("Sallman"). Applicants note that although the Office Action refers to "Steinberg et al.," a previous telephone conference with the examiner on September 25, 2002 clarified and confirmed that "Steinberg et al." refers to Wen. For purposes of this response, reference is made only to Wen.

According to the Office Action, Wen et al. "teach the use of brimonidine and fibroblast growth for the treatment of diseases or conditions caused by injury or death of retinal photoreceptors." It is further stated that it would have been obvious to add "non-steroidal anti-inflammatory agents to brimonidine," (referring to Sallman), for reasons mentioned in the previous Office Action.

Claim 1 has been amended to recite "a method of inhibiting a degenerative condition of a retinal photoreceptor cell, which condition is caused by damage, disruption, or degeneration of an RPE cell or a Muller cell...." Applicants respectfully disagree that it would have been obvious from the teachings of Wen to use brimonidine for treatment of photoreceptor degenerations caused by damage, disruption, or degeneration of RPE or Muller cells, for the reasons set forth below.

The Office Action asserts that the Wen reference "makes clear that brimonidine and growth factor have been previously used for the treatment of conditions caused by the injury or death to the retinal photoreceptors." Although it is not expressly stated, the Office Action implies that it would have been obvious to those in the field of photoreceptor degeneration to treat any type of photoreceptor degeneration with brimonidine, given the teachings of Wen.

To establish a *prima facie* case of obviousness, there must be 1) some suggestion or motivation to those of skill in the art at the time of the invention to modify the references or combine the reference teachings, 2) reasonable expectation of success, and 3) the combined references must teach or suggest every element of the claims. See MPEP § 2143.

Photoreceptor Degeneration Is Caused By Many Different Mechanisms.

It was well known in the art at the time of the applicants' invention that there are myriad causes of photoreceptor degeneration. Many of them are hereditary, and can involve mutations

in specific genes in either 1) the photoreceptors themselves or 2) the retinal pigment epithelial (RPE) cells. (See, for example, Sullivan LS and Daiger SP, Inherited retinal degeneration: exceptional genetic and clinical heterogeneity, Mol. Med. Today 2: 380-386, 1996.) Furthermore, non-hereditary forms of photoreceptor degeneration can be caused by a variety of insults to photoreceptors and other cell types as well. In short, many forms of photoreceptor degeneration are caused by many types of defects, including those in cell types other than photoreceptors. In the latter conditions, degeneration of the photoreceptors occurs as a secondary consequence of the primary insult to the other cell type.

No Expectation of Success Existed Because the Wen Patent Shows Photoreceptor Degeneration Caused by Only One Mechanism, i.e., Light Damage to Photoreceptors.

Given the large variety of known photoreceptor degenerative conditions, (many of which are caused by problems in cell types other than photoreceptors), those of skill in the art would not have been motivated to combine the teachings of Wen and Sallman to use brimonidine to treat photoreceptor degenerations caused by mechanisms other than light damage to photoreceptors. Nor would they have had a reasonable expectation of success, for the following reasons.

The Wen patent demonstrated a protective effect of two agents, i.e., clonidine and xylazine, in photoreceptors damaged by one mechanism alone, i.e., excessive light. As discussed in applicants' previous response dated May 14, 2002, the Wen results were obtained using a model of photoreceptor degeneration induced by exposing the retina to very high light levels. The Wen patent does not demonstrate a protective effect of brimonidine, or any other agent, on photoreceptor degenerations caused by 1) any mechanism other than light damage, 2) any mechanism involving a genetic defect in a photoreceptor cell, or 3) any mechanism caused by

damage, disruption, or degeneration of a cell type other than the photoreceptors, for example, photoreceptor degeneration caused by damage, disruption, or degeneration of an RPE cell or a Muller cell.

Applicants' Results Show That Brimonidine Inhibits Photoreceptor Degeneration Caused By Dysfunctional (or Absent) RPE Cells.

The studies described in Wen are in marked contrast to those performed by the inventors. In applicants' experiments, damage to the photoreceptors was inflicted by depriving the photoreceptors of their underlying supportive layer in the retina, i.e., the layer of RPE cells. It is well known that RPE cells provide essential support for the photoreceptors, and that damage or degeneration of the RPE cells can result in many types of consequential photoreceptor degeneration, the most common being are age-related macular degeneration and retinal detachment. Wen does not teach the use of brimonidine for photoreceptor degeneration caused by deprivation of, or damage to, the RPE cells.

The effect of brimonidine in applicant's system was to promote normal photoreceptor structure and function in a damaging condition caused by absence of the RPE cells. This is evidenced in the specification by support of normal membrane assembly and production of opsin by photoreceptors, in absence of RPE, but in the presence of brimonidine. Compare, for example, Figs. 3A, 4A and 5A of the application, reproduced herein and attached as "Exhibit A." Exhibit A shows normal photoreceptor structure in the presence of RPE (Fig. 3A), degeneration in the absence of RPE (Fig. 4A) and nearly normal photoreceptors in the absence of RPE, but in the presence of brimonidine (Fig. 5A). Further evidence of normal retinal architecture and gene expression was exhibited by the Muller cells of brimonidine-treated retinas devoid of RPE. (See Figs. 7,8.)

Applicants' results show that brimonidine inhibited photoreceptor degeneration following separation of the retina from the RPE. Accordingly, as stated in the specification on p. 20, lines 27-29, applicants' work demonstrates that "brimonidine may be an effective therapeutic agent for certain forms of retinal degenerations and other conditions where disruption of RPE integrity may lead to permanent loss of photoreceptor function." Such conditions are described in the specification (§§ 4.4.2 - 4.4.4) and include, but are not limited to, photoreceptor degeneration resulting from removal of the RPE (for example, by retinal detachment), photoreceptor degeneration resulting from mutations in RPE genes, and age-related macular degeneration. Claims 1, 5, and 13 have been amended to clarify applicants' discovery of the particular types of photoreceptor degeneration that can be treated with brimonidine and related compounds.

The Office Action asserts that Sallman teaches the use of secondary active ingredients, wetting agents and ophthalmic carriers in an ophthalmic formulation for treatment of inflammatory conditions of the eye. In view of the inapplicability of the primary reference (i.e., Wen) to photoreceptor degenerations caused by damage, disruption, or degeneration of the RPE or Muller cells, the rejection under 35 U.S.C. § 103, based on the combination of Wen and Sallman, is rendered moot. Accordingly, applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

Conclusion

This paper is intended to be fully responsive. The currently pending claims are supported throughout the specification and are patentable over the prior art. No new matter has been added. This application is believed to be in full condition for allowance, and such action is respectfully requested.

This amendment is believed to be timely filed. The Commissioner is hereby authorized to charge any underpayment or credit any overpayment of fees under 37 C.F.R. § 1.16 or 1.17 as required by this paper to Deposit Account 50-0951.

The examiner is requested to call the undersigned if clarification is needed on any matter within this amendment, or if the examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

AKERMAN SENTERFITT

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